

ISSN 0307 6938

Volume 12 Number 2 March 1987



Clinical and Experimental Dermatology

Edited by
W.A.D. GRIFFITHS

Dr. Reddy's Laboratories, Ltd., et al.
v.
Galderma Laboratories, Inc.
IPR2015

Stevens-Johnson syndrome due to tetracyclines—a case report (doxycycline) and review of the literature

R.K.CURLEY AND J.L.VERBOV *St George's Hospital, Tooting and *Royal Liverpool Hospital, Prescot Street,* Liverpool L7 8XP, UK*

Accepted for publication 26 September 1986

Summary

A young adult female with Stevens-Johnson syndrome due to doxycycline is described. Other reports of Stevens-Johnson syndrome due to tetracyclines are also reviewed.

Erythema multiforme is an inflammatory skin reaction often recurrent and of unknown cause. It may be precipitated by various agents, including drugs and infections and occur at any age, but is most common in young adults. The lesions present may be of many types but usually one type predominates. It was first described by Hebra in 1860.¹ The most severe form of erythema multiforme was described in 1922 by Stevens and Johnson² as an eruptive fever associated with stomatitis and severe conjunctivitis. The best-documented drug association with Stevens-Johnson syndrome is long-acting sulphonamides.^{3,4}

Case Report

A 34-year-old woman who had been treated 6 years previously for late secondary syphilis but had not received a full course of treatment because of an allergic reaction to penicillin, was given a 15-day course of doxycycline 300 mg daily, as a precautionary measure in late November–December 1985, in view of unchanged raised serology titres. The titres had been checked during routine pregnancy screening in October 1985. The patient requested a termination of pregnancy and received a 5-day course of tetracycline at that time without ill-effect (the routine post-abortion procedure for all patients at that hospital). The day after completing the 15-day course of doxycycline she developed burning of her eyes and dysuria and, after a further 2 days, the eruption of erythema multiforme. She was admitted urgently to hospital five days after discontinuation of the drug. Large bullae appeared soon after admission in addition to widespread small discrete papular and vesicular skin lesions and extensive mouth, genital, and eye

involvement. Investigations revealed a normal full blood count and serum electrolytes, and a normal CXR. A skin biopsy confirmed the diagnosis of erythema multiforme. Paired sera for Herpes simplex, Mycoplasma pneumoniae, and Psittacosis showed no significant increase in titres.

She was treated with intravenous fluid replacement, oral erythromycin, intravenous hydrocortisone 400 mg daily, followed by a tapering course of oral prednisolone, and was nursed on a ripple bed. Eye lesions were treated with chloramphenicol eye ointment and prednisolone/neomycin (Predsol-N) eye drops. Mouth lesions were treated initially with benzydamine hydrochloride oral rinse (Difflam) and later chlorhexidine gluconate (Corsodyl) mouth wash. She made a gradual recovery, and was discharged home 25 days after admission, receiving a mouth wash containing triamcinolone 1 mg t.d.s. for persistent gingival and buccal ulceration. At the time of discharge she showed guttate macular hypopigmented areas over the backs of both forearms, and post-inflammatory hyperpigmentation over her cheeks and back. This was improving when seen at follow-up one, and three months later. She had residual mild conjunctival scarring, and epiphora affecting both eyes due to scarring of the puncta: the latter required minor ophthalmological surgery.

Discussion

Tetracyclines are widely used in dermatology patients in the management of acne and rosacea. Severe adverse reactions are uncommon. The principal side-effects, i.e. nausea, vomiting, and sometimes diarrhoea, are due to retention of the antibiotic in the bowel.⁵ Other effects include deposition in calcifying bone, and staining of the deciduous teeth⁶, liver damage⁷, renal toxicity^{8,9}, oesophageal ulceration¹⁰ and raised intracranial pressure.¹¹ Skin reactions are relatively rare. Arndt and Jick predicted a cutaneous reaction rate of not greater than 0.3% for tetracycline (upper confidence limit 95%) compared with an observed rate of 5.9% for co-trimoxazole, and 5.2% for ampicillin.¹² In addition to erythema multi-

Correspondence: Dr J.L. Verbov, Consultant Dermatologist, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.

forme, fixed drug eruption^{13,14}, toxic epidermal necrolysis¹⁵, exanthematic eruptions, urticaria, angioedema and purpura¹⁶ have been reported. Dimethylchlorotetracycline and, to a lesser degree, other tetracyclines, are phototoxic.^{17,18}

There are scanty reports in the literature of tetracyclines causing Stevens-Johnson syndrome. Up to February 1986 the Committee on Safety of Medicines had reports of five cases of Stevens-Johnson syndrome due to tetracyclines, but this is, of course, likely to be an underestimate because of lack of reporting of adverse effects. Caldwell and Cluff¹⁹, in a 3-year prospective study of adverse reactions to antimicrobial agents, described six cases of Stevens-Johnson syndrome of which two were caused by tetracycline. Ting and Adam²⁰ reported 34 cases occurring over a 16-year period of which four were attributed to tetracycline. Tetracycline has, in some reports, been given in addition to other drugs. Of the two patients reported by Claxton²¹, who had received tetracycline prior to the development of Stevens-Johnson syndrome, one had also received sulphamethoxypyridazine: whether the other patient had also received further drugs is not stated. Gorbachev and colleagues²² described a patient who developed Stevens-Johnson syndrome after a combination of tetracycline, penicillin, and streptomycin. In addition, patients are often prescribed antibiotics for pre-existing infection, and it is not always possible to decide which is the aetiological factor. Wasserman and Glass²³ described a patient who developed Stevens-Johnson syndrome after taking tetracycline phosphate capsules, but were also able to demonstrate an eight-fold rise in titre of antibodies to type A Influenza virus. Ström²⁴, in a survey of 266 patients with febrile mucocutaneous syndromes, identified one patient who was treated for an infection with a tetracycline, and two patients who were treated with tetracycline in combination with penicillin or sulphonamide. Prusek and colleagues²⁵ described a case of Stevens-Johnson syndrome associated with bone marrow aplasia occurring in a child treated for bronchitis with methacycline (Rondomycin).

Doxycycline (6-Deoxy-5 β -hydroxytetracycline monohydrate), is a long-acting tetracycline which is readily absorbed from the gastro-intestinal tract and has adverse effects similar to the other tetracyclines. We are unaware of any published reports, in the English literature, of Stevens-Johnson syndrome following use of this antibiotic. Albengres and co-workers²⁶ described a case of recurrent Stevens-Johnson syndrome which occurred after taking doxycycline which was also precipitated by hexacycline (tetracycline phosphate complex).

References

1. Hebra F. In: R. Virchow, ed. *Handbuch der Speciellen Pathologie und Therapie* 1860; Vol. 3, Erlangen: Enke, p 198.
2. Stevens AM, Johnson FC. A new eruptive fever associated with

- stomatitis and ophthalmia. *American Journal of Diseases of Children* 1922; 24: 526-533.
3. Carroll OM, Bryan PA, Robinson RJ. Stevens-Johnson syndrome associated with long-acting sulfonamides. *Journal of the American Medical Association* 1966; 195: 691-693.
4. Böttiger LE, Strandberg I, Westerholm B. Drug-induced febrile mucocutaneous syndrome. *Acta Medica Scandinavica* 1975; 198: 229-233.
5. Verbov JL. Tetracyclines in Dermatology. *Transactions of the St John's Hospital Dermatological Society* 1969; 1: 78-84.
6. Stewart DJ. Tetracyclines: their prevalence in children's teeth. *British Dental Journal* 1968; 124: 318.
7. Peters RL, Edmondson HA, Mikkelsen WP, Tatter D. Tetracycline-induced fatty liver in nonpregnant patients: a report of six cases. *American Journal of Surgery* 1967; 113: 622-632.
8. Lew HT, French SW. Tetracycline nephro-toxicity and non-oliguric acute renal failure. *Archives of Internal Medicine* 1966; 118: 123-128.
9. Phillips ME, Eastwood JB, Curtis JR, Gowe, PE, De Wardener HE. Tetracycline poisoning in renal failure. *British Medical Journal* 1974; 2: 149-151.
10. Crowson TD, Head LH, Ferrante WA. Esophageal ulcers associated with tetracycline therapy. *Journal of the American Medical Association* 1976; 235: 2747-2748.
11. Bhowmick BK. Benign intracranial hypertension after antibiotic therapy. *British Medical Journal* 1972; 3, 30-30.
12. Arndt KA, Jick H. Rates of cutaneous reactions to drugs. *Journal of the American Medical Association* 1976; 235: 918-923.
13. Pasricha JS. Drugs causing fixed eruptions. *British Journal of Dermatology* 1979; 100: 183-185.
14. Jolly HW, Sherman IJ, Carpenter CL, Nesbitt LT, Meek TJ. Fixed drug eruptions to tetracyclines. *Archives of Dermatology* 1978; 114: 1484-1485.
15. Lowney ED, Baublis JV, Kreye GM, Harrell ER, McKenzie AR. The scaled skin syndrome in small children. *Archives of Dermatology* 1967; 95: 359-369.
16. Bruinsma W. Adverse reaction profiles of drug eruptions. *Dermatologica* 1972; 145: 377-388.
17. Cullen SI, Catalano PM, Helfman RJ. Tetracycline sun sensitivity. *Archives of Dermatology* 1966; 93: 77.
18. Epstein JH, Tuffanelli DL, Seibert JS, Epstein WL. Porphyria-like changes induced by tetracycline hydrochloride photosensitization. *Archives of Dermatology* 1975; 112: 661-666.
19. Caldwell JR, Cluff LE. Adverse reactions to antimicrobial agents. *Journal of the American Medical Association* 1974; 230: 77-80.
20. Ting HC, Adam BA. Stevens-Johnson Syndrome: A review of 34 cases. *International Journal of Dermatology* 1985; 24: 587-591.
21. Claxton RC. A review of 31 cases of Stevens-Johnson syndrome. *The Medical Journal of Australia* 1963; 50: 963-967.
22. Gorbachev VV, Bronovets IN, Vetokhin VI, Chugunkina SB, Karachan NZ. Stevens-Johnson syndrome as a complication of antibacterial therapy. *Terapevticheskii Arkhiv (Moskva)* 1972; 44: 106-108. (Original paper in Russian.)
23. Wasserman E, Glass WI. Stevens-Johnson syndrome. *Archives of Internal Medicine* 1959; 104: 125-130.
24. Ström J. Aetiology of febrile muco-cutaneous syndromes with special reference to the provocative role of infections and drugs. *Acta Medica Scandinavica* 1977; 201: 131-136.
25. Prusek W, Nawrocka E, Kozierowska B, Kosinski S. Exudative erythema with bone marrow aplasia after treatment with rondomycin. (Original paper in Polish.) *Polski Tygodnik Lekarski* 1980; 35: 503-504.
26. Albengres E, Guillaume JC, Chevais M, Riant P, Touraine R, Tillement JP. Ectodermose pluriorificielle répétitive lors de traitements successifs par des tetracyclines: A propos d'un cas. *Therapie* 1983; 38: 577-579.